

Microalbuminuria Modifies the Mortality Risk Associated With Electrocardiographic ST-T Segment Changes

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OBJECTIVES	We sought to investigate whether microalbuminuria, a proposed marker of generalized vascular damage, enhances the prognostic value of ST-T segment changes for all-cause and cardiovascular mortality in the general population.
BACKGROUND	ST-T segment changes on the rest electrocardiogram (ECG) predict mortality in the general population. However, the excess risk seems to be low, particularly in nonhospitalized populations with a low cardiovascular risk profile.
METHODS	In a population of 7,330 male and female subjects, a total of 89 deaths (1.2%) occurred during a median three-year follow-up. In 69 of these, the cause of death was obtained from the Central Bureau of Statistics: 25 subjects died of cardiovascular causes (36%). Using computerized Minnesota coding, ST-T segment changes were coded as 4.1-4 and 5.1-4. Microalbuminuria was defined as a urinary albumin excretion of 30 to 300 mg per 24 h.
RESULTS	The combination of ST-T segment changes and microalbuminuria showed a higher hazard ratio (HR) for all-cause mortality (HR 8.6 [95% confidence interval [CI] 4.8 to 15.2, $p < 0.0001$), as compared with ST-T segment changes in the absence of microalbuminuria (HR 1.3 [95% CI 0.7 to 2.5]), which was independent of other cardiovascular risk factors (HR 3.3 [95% CI 1.5 to 7.1], $p = 0.002$). The combination showed a higher HR when only cardiovascular deaths were taken into account, as compared with all-cause mortality (HR 24.5 [95% CI 7.9 to 76.0], $p < 0.0001$), which also counted for ST-T segment changes alone (HR 4.4 [95% CI 1.4 to 14.5], $p = 0.02$). After controlling for other risk factors, the HRs were 10.4 (95% CI 2.5 to 43.6, $p = 0.001$) for the combination and 2.7 (95% CI 0.6 to 12.3) for ST-T segment changes alone.
CONCLUSIONS	This study suggests that, in subjects with ST-T segment changes on their rest ECG, microalbuminuria could identify those at increased risk of all-cause and cardiovascular mortality. (J Am Coll Cardiol 2002;40:1401-7) © 2002 by the American College of Cardiology Foundation

The rest electrocardiogram (ECG) is a useful tool to identify subjects at increased cardiovascular risk in the general population (1,2). ST segment and T wave (ST-T) changes, suggestive of myocardial ischemia, are associated with an increased risk of total and cardiovascular mortality (3,4). However, in a number of cases, particularly in low-risk populations, these ST-T segment changes on the rest ECG are not specific for coronary artery disease (5). Therefore, additional easy-to-obtain markers of (subclinical) cardiovascular disease are mandatory to improve cardiovascular risk profiling.

Microalbuminuria, usually diagnosed when there is a urinary albumin excretion of 30 to 300 mg per 24 h (6), has been hypothesized to be an indicator of generalized vascular

dysfunction (7). In diabetic as well as nondiabetic populations, microalbuminuria has been demonstrated to predict cardiovascular disease, independent of traditional cardiovascular risk factors (8,9). Moreover, we previously found in the Prevention of Renal and Vascular End-stage Disease (PREVEND) study that microalbuminuria was independently associated with ischemic ECG abnormalities (10). Therefore, microalbuminuria might identify subjects at particular risk of ischemic heart disease and to enhance the utility of ECG testing.

We hypothesized that microalbuminuria improves the prognostic value of ECG markers suggestive of myocardial ischemia. Therefore, we assessed the prognostic value of ST-T segment changes on the rest ECG, taking the presence of microalbuminuria into account, for all-cause and cardiovascular mortality in the population at large.

METHODS

Study design and population. The population analyzed in this study was obtained from the PREVEND study. The PREVEND study was designed to investigate the natural course of microalbuminuria and its relation to renal and

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Abbreviations and Acronyms

CI	= confidence interval
ECG	= electrocardiogram
HR	= hazard ratio
PREVEND	= Prevention of REnal and Vascular ENd-stage Disease study

cardiovascular disease in the general population. The study cohort included male and female inhabitants, aged 28 to 75 years, of the city of Groningen, the Netherlands (11). These inhabitants were asked to send in a morning urine sample. A sample population consisting of all subjects with an albumin concentration of >10 mg/l in the morning urine sample, completed with a randomly selected sample of the remainder of the population (morning urine albumin excretion <10 mg/l), made two visits to an outpatient clinic. Subjects using insulin or those who were pregnant were excluded. The visits consisted of anthropometric measurements, blood pressure measurements for 10 min with an automatic Dinamap XL model 9300 series device (Johnson-Johnson Medical Inc., Tampa, Florida), collection of two 24-h urine samples, ECG recording, and obtainment of fasting blood samples. Furthermore, all participants completed a questionnaire on demographic data and cardiovascular and renal history. Because the objective of this study was to assess risk factors for cardiovascular end-stage disease, all analyses were performed after excluding subjects with clinical or ECG evidence, defined by Minnesota codes 1.1 and 1.2, of a previous myocardial infarction.

A total of 8,592 subjects made two visits to the outpatient clinic. For the present study, 18 subjects were excluded because of missing albuminuria data, 433 because of the presence of hematuria or leukocyturia, 117 because of macroalbuminuria, and 70 because of missing ECG data. At the outpatient clinic, two participants appeared to use insulin and were excluded. Furthermore, 622 subjects were diagnosed with a previous myocardial infarction and were also excluded. Finally, 7,330 subjects were eligible for analysis. The median follow-up period was 987 days (range 2 to 1,229). During the follow-up period, 89 deaths (1.2%) occurred. In 69 of these, the cause of death was obtained from the Central Bureau of Statistics: 25 subjects died of cardiovascular causes (36%).

All participants gave written, informed consent. The PREVEND study was approved by the local medical Ethics Committee and conducted in accordance with the guidelines of the Declaration of Helsinki.

Mortality data. The vital status was checked through the municipal register. Mortality follow-up was initiated in September 1997 and followed until February 2001. The cause of death was obtained by linking the number of the death certificate to the primary cause of death, as coded by a physician of the Central Bureau of Statistics. Causes of death were coded according to the tenth revision of the International Classification of Diseases (ICD-10). Cause-

specific end points used in the analyses were all-cause mortality (ICD A00-Y89) and cardiovascular mortality (ICD I00-I99). In the analyses of specific causes of death, follow-up information until September 2000 was used. The census date was the date on which the information was obtained from the municipal registry (for the living) or the date of death. If a person had moved to an unknown destination, the date on which the person was dropped from the municipal registry was used as the census date.

Laboratory methods. Urinary volume and albumin were measured in each collection. Urinary albumin concentrations were determined by nephelometry with a threshold of 2.3 mg/l and intra-assay and inter-assay coefficients of variation of $<4.3\%$ and $<4.4\%$, respectively (Dade Behring Diagnostic, Marburg, Germany). Leukocyte and erythrocyte counts were determined by urine sticks (Nepthur+leuco, Boehringer Mannheim, Mannheim, Germany). Serum glucose and serum cholesterol were determined by Kodak Ektachem dry chemistry (Eastman Kodak, Rochester, New York).

Electrocardiography. Standard 12-lead ECGs were recorded with Cardio Perfect equipment (Cardio Control, Delft, The Netherlands), stored digitally, and classified according to the Minnesota code, using the computer program MEANS (Modular ECG Analysis System) (12,13). Signal analysis and classification of MEANS have been extensively evaluated in both clinical and general population samples (14). Results show that the program is as good as or better than the human reader for sensitivity and specificity of all Minnesota Code categories (12). The sensitivity for ST segment depression was 96.0% for visual coding and 96.8% for computer coding, whereas the specificity was 98.3% and 99.4%, respectively. For T wave items, the sensitivity was 98.3% for visual coding and 96.0% for computer coding, whereas the specificity was 93.5 and 99.2, respectively. ST-T segment changes were defined by Minnesota codes 4.1-4 and 5.1-4 (3).

Definitions. The urinary albumin excretion rate was measured as the mean of two 24-h urine collections, and microalbuminuria was diagnosed at 30 to 300 mg per 24 h. Albumin measurements were considered unreliable when >75 leukocytes per μl or >50 erythrocytes per μl were measured in the urine. Conventional cardiovascular risk indicators were: age >60 years, male gender, hypertension (diastolic blood pressure ≥ 90 mm Hg or systolic blood pressure ≥ 140 mm Hg or current antihypertensive treatment), hypercholesterolemia (total serum cholesterol ≥ 6.5 mmol/l or the use of lipid-lowering medication), diabetes mellitus (fasting plasma glucose levels ≥ 7.0 mmol/l or nonfasting glucose ≥ 11.1 mmol/l [5.2% of the study population was not fasting] or the use of antidiabetic drugs), overweight (body mass index ≥ 27 kg/m²), cardiovascular family history (first-grade relatives had established a cardiovascular event before 55 years of age), and smoking (stopped smoking less than a year ago or current cigarette smoking).

Table 1. Baseline Characteristics

	No ST-T Segment Changes/ No Microalbuminuria (n = 5,424 [74%])	No ST-T Segment Changes/ Microalbuminuria (n = 662 [9%])	ST-T Segment Changes/ No Microalbuminuria (n = 1,021 [14%])	ST-T Segment Changes/ Microalbuminuria (n = 223 [3%])	Total (n = 7,330)
Age (yrs)	47 ± 12	53 ± 12	51 ± 13	59 ± 12†	48 ± 12
Gender (male)	48%	62%	49%	69†	50%
Urinary albumin excretion (mg/24 h)*	8.0 (5.9–12.0)	52.4 (37.8–88.5)	8.8 (6.2–13.1)	55.3 (39.8–86.0)†	8.9 (6.2–15.9)
Diastolic blood pressure (mm Hg)	73 ± 9	78 ± 10	75 ± 10	83 ± 12†	74 ± 10
Systolic blood pressure (mm Hg)	125 ± 17	139 ± 22	133 ± 22	153 ± 24†	128 ± 20
Hypertension	23%	53%	39%	78†	29%
Cholesterol (mmol/liter)	5.6 ± 1.1	5.9 ± 1.2	5.7 ± 1.1	5.9 ± 1.1†	5.6 ± 1.1
Hypercholesterolemia	22%	32%	26%	35†	24%
Body mass index (kg/m ²)	25.7 ± 4.0	27.7 ± 4.9	25.7 ± 4.1	28.1 ± 4.6†	26.0
Overweight	32%	51%	33%	59†	35%
Glucose (mmol/liter)	4.7 ± 0.9	5.4 ± 1.9	4.9 ± 1.2	5.7 ± 2.4†	4.9 ± 1.1
Diabetes mellitus	2%	10%	4%	11†	3%
Smoking	39%	42%	34%	36%	38%
Cardiovascular family history	22%	26%	24%	20%	22%

*Median value (25th–75th percentile). †p < 0.001 for trend. Continuous variables are given as the mean value ± SD.

Statistical analysis. To evaluate the effect of ST-T segment changes with or without microalbuminuria, four groups were created. The first group, which served as the reference group, consisted of subjects with no ST-T segment changes and no microalbuminuria; the second group of subjects had no ST-T segment changes and present microalbuminuria; the third group of subjects had ST-T segment changes and no microalbuminuria; and the fourth group of subjects had both ST-T segment changes and microalbuminuria. Survival was estimated by the Kaplan-Meier product-limit method, compared with the log-rank test, and stratified for the four groups. This was performed separately for survival free of all-cause mortality and cardiovascular mortality. All-cause and cardiovascular mortality risks and 95% confidence intervals (CIs) were estimated with Cox proportional hazards regression analysis. In the case of cardiovascular mortality, patients who died of causes other than coronary heart disease were censored at the time of their death. The assumption of proportional hazards was checked by complementary log plots. Relative hazard ratios (HRs) for each specific co-variate of the final models were computed as the exponential of the regression coefficient. The contribution of two-factor interactions with the model was evaluated for variables that showed significant ($p < 0.05$) main effects. Three different models were used: model 1 was unadjusted; model 2 was adjusted for age >60 and male gender; and model 3 was adjusted for age >60, male gender, and established cardiovascular risk factors (e.g., hypertension, hypercholesterolemia, diabetes mellitus, overweight, cardiovascular family history, smoking). A two-sided p value of <0.05 was considered statistically significant. Analyses were performed using the statistical package SPSS version 9.0 (Chicago, Illinois).

RESULTS

The prevalence of all ST-T segment changes together was 16.9%. The prevalence of more severe ST-T segment

changes (codes 4.1-2 and 5.1-2) was 7%, whereas that for less severe ST-T segment changes (codes 4.3-4 and 5.3-4) was 9.9%. The baseline characteristics of the total population and those stratified by ST-T segment changes and microalbuminuria are listed in Table 1. Microalbuminuria identifies subjects with an increased cardiovascular risk, particularly in combination with ST-T segment changes. Subjects with microalbuminuria and ST-T segment changes were older and more often male and had a high prevalence of hypertension, hypercholesterolemia, obesity, and diabetes mellitus. Smoking and cardiovascular family history was approximately equal among the four groups.

Table 2 shows the incidence of all-cause and cardiovascular mortality. Both were low in the group with no ST-T segment changes and no microalbuminuria, and highest in the group with both ST-T segment changes and microalbuminuria.

The overall relative risk of total mortality associated with ST-T segment changes in the population was 2.1 (unadjusted; 95% CI 1.4 to 3.3, $p = 0.001$) and 1.3 (adjusted for cardiovascular risk factors; 95% CI 0.7 to 2.2, $p = 0.4$), whereas the overall relative risk of microalbuminuria was 4.3 (unadjusted; 95% CI 2.8 to 6.6, $p < 0.001$) and 2.3 (adjusted; 95% CI 1.3 to 4.1, $p = 0.004$). Figure 1 shows Kaplan-Meier survival curves with respect to all-cause and cardiovascular mortality in the four groups. Log-rank sta-

Table 2. Incidence of Deaths From Any Cause (A) and Cardiovascular Causes (B)

A	No Microalbuminuria	
	Microalbuminuria	Microalbuminuria
ST-T segment changes	16 (7.2%)	11 (1.1%)
No ST-T segment changes	17 (2.6%)	45 (0.8%)

B	No Microalbuminuria	
	Microalbuminuria	Microalbuminuria
ST-T segment changes	6 (2.7%)	5 (0.5%)
No ST-T segment changes	8 (1.3%)	6 (0.1%)

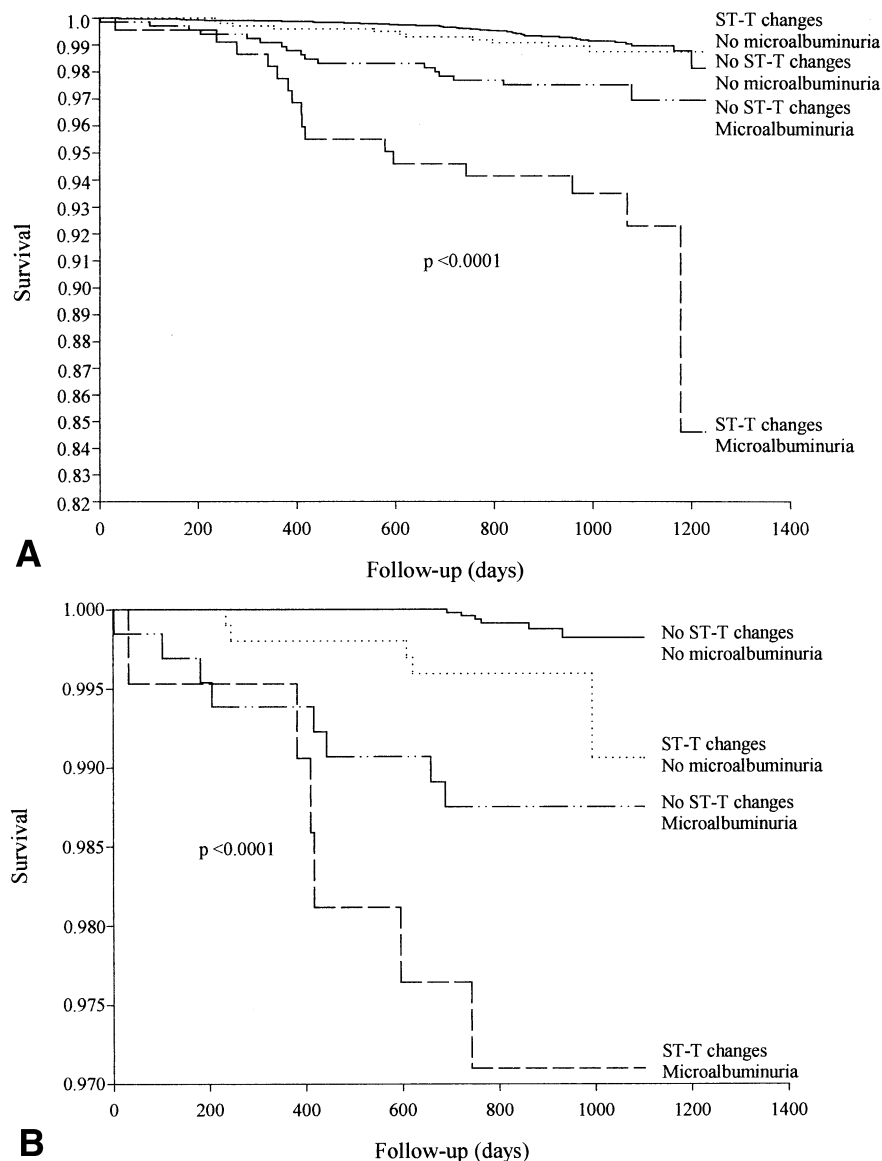


Figure 1. Kaplan-Meier estimates of all-cause (A) and cardiovascular (B) mortality in the four groups.

tistics were highly significant for both all-cause and cardiovascular mortality ($p < 0.001$). The significance of the differences in all-cause and cardiovascular mortality risk among the four groups was tested by Cox regression analysis, using the group with no ST-T segment changes and no microalbuminuria as the reference group (Table 3). The combination of ST-T segment changes and microalbuminuria showed the highest HR for all-cause mortality, which was independent of other cardiovascular risk factors. In addition, microalbuminuria alone was predictive of all-cause mortality, although it was not independent of the other risk factors. ST-T segment changes did not significantly predict all-cause mortality. The combination showed a higher HR when only cardiovascular deaths were taken into account, as compared with all-cause mortality, which also counted for microalbuminuria alone. ST-T segment changes in the absence of microalbuminuria were predictive

of cardiovascular mortality. However, this was not independent of other risk factors.

We also explored the additional impact of classic cardiovascular risk factors related to ST-T segment changes on mortality (Fig. 2). This demonstrated that the combination of ST-T segment changes and microalbuminuria had the highest predictive value for mortality.

DISCUSSION

This study demonstrates that in a nonhospitalized population, microalbuminuria increases the mortality risk associated with ST-T segment changes on the rest ECG. The effect is independent of cardiovascular risk factors and seems even greater for cardiovascular mortality. The additive value of microalbuminuria to ST-T segment changes was higher

Table 3. Hazard Ratios (95% Confidence Intervals) for All-Cause and Cardiovascular Mortality Stratified by ST-T Segment Changes and Microalbuminuria

	All-Cause Mortality					
	Model 1*		Model 2†		Model 3‡	
No ST-T segment changes/no microalbuminuria	1.0		1.0		1.0	
No ST-T segment changes/microalbuminuria	3.1 (1.8–5.5)	p = 0.0001	2.0 (1.2–3.6)	p = 0.01	1.8 (0.9–3.6)	
ST-T segment changes/no microalbuminuria	1.3 (0.7–2.5)		0.9 (0.5–1.8)		0.9 (0.4–1.9)	
ST-T segment changes/microalbuminuria	8.6 (4.8–15.2)	p < 0.0001	3.9 (2.1–7.1)	p < 0.0001	3.3 (1.5–7.1)	p = 0.002
	Cardiovascular Mortality					
	Model 1*		Model 2†		Model 3‡	
No ST-T segment changes/no microalbuminuria	1.0		1.0		1.0	
No ST-T segment changes/microalbuminuria	11.0 (3.8–31.6)	p < 0.0001	7.1 (2.4–20.9)	p = 0.0004	4.5 (1.1–18.9)	p = 0.04
ST-T segment changes/no microalbuminuria	4.4 (1.4–14.5)	p = 0.01	3.3 (1.0–11.1)	p = 0.05	2.7 (0.6–12.3)	
ST-T segment changes/microalbuminuria	24.5 (7.9–76.0)	p < 0.0001	11.1 (3.4–36.4)	p = 0.0001	10.4 (2.5–43.6)	p = 0.001

*Unadjusted. †Adjusted for age >60 years and male gender. ‡Adjusted for age >60 years, male gender, hypertension, hypercholesterolemia, overweight, diabetes mellitus, cardiovascular family, history, and smoking.

than that of established cardiovascular risk factors, such as hypertension and hypercholesterolemia.

The ECG can be used to determine the presence of ischemic heart disease in a population at large (10). In three Chicago-based epidemiologic studies, ECG abnormalities, particularly major abnormalities, were independently associated with cardiovascular mortality and morbidity (15). Also, both the Honolulu Heart Program and the Busseton Study showed an independent contribution of major and minor ECG abnormalities for coronary heart disease (1,2). Furthermore, in the Framingham study, nonspecific ST segment and T wave abnormalities on the rest ECG were associated with an increased risk of cardiovascular disease (16). These results have been validated in various other epidemiologic studies for both men and women (4), as well as for different races (17). However, the excess risk seems to

be small, particularly in nonhospitalized populations with a low cardiovascular risk profile (5). Although ST-T segment changes in subjects with a previous myocardial infarction are associated with a 10-fold risk of coronary heart disease, the risk was only twofold in subjects without known ischemic heart disease (3). ST-T segment changes on the rest ECG might be due to causes other than myocardial ischemia (e.g., hyperventilation, emotional strain, recent food ingestion) (18). This limits the applicability of the rest ECG for screening purposes in the population at large. Additional markers of (subclinical) atherosclerotic disease may enhance stratification for cardiovascular disease in order to adequately target preventive strategies. For example, the combination of ST-T segment changes and hypercholesterolemia did improve the identification of male subjects at risk of coronary heart disease in the West of Scotland Coronary Prevention study (19).

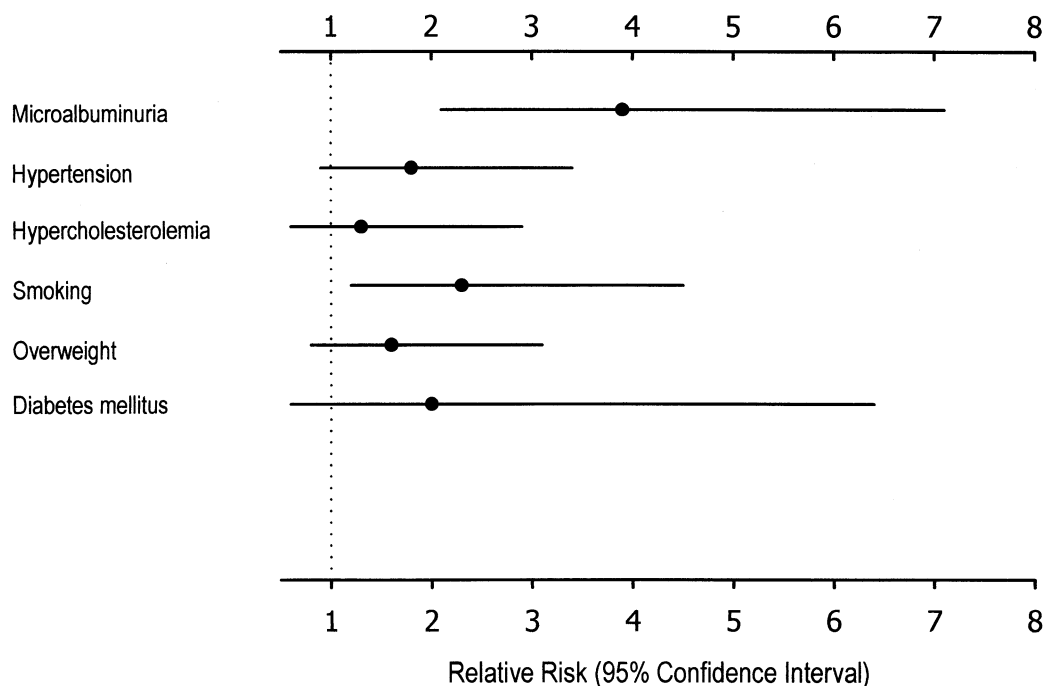


Figure 2. Relative risk of the combination ST-T segment changes and cardiovascular risk indicators for all-cause mortality adjusted for age and gender.

The prognostic value of microalbuminuria for cardiovascular disease was first established in patients with diabetes mellitus (8). In nondiabetic subjects, the results from several studies have indicated that microalbuminuria is a marker of cardiovascular risk factors (11,20,21) and (subclinical) cardiovascular disease (10,22). Moreover, several studies have demonstrated that microalbuminuria is an independent predictor of cardiovascular morbidity and mortality in nondiabetic populations (9,23,24). In the present study, we demonstrate a major increase in mortality in the subset of subjects with both ST-T segment changes and microalbuminuria. It has been postulated that microalbuminuria indicates increased vascular or endothelial permeability that is not only restricted to renal vessels, which could promote foam-cell formation and atherogenesis by increased leakage of lipoprotein particles, for example, into the vessel wall (7). An increased transcapillary albumin excretion rate (25), an increased plasma level of von Willebrand factor (26), and an attenuated endothelium-dependent response to vasodilator stimuli (27) in subjects with microalbuminuria support this hypothesis. Therefore, individuals with ST-T segment changes in addition to microalbuminuria could be at increased risk of enhanced progression of atherosclerosis and subsequently mortality. Moreover, this hypothesis might explain why microalbuminuria without ST-T segment changes also predicts cardiovascular mortality.

A few limitations should be mentioned. First, only a limited number of (cardiovascular) deaths were observed, explaining the large confidence intervals of the HRs. Moreover, in 20 subjects, we did not have information on the cause of death. Therefore, we should be cautious not to overemphasize the predictive value of the combination of ST-T segment changes and microalbuminuria, particularly on cardiovascular mortality. Second, the relatively short follow-up period could explain the fact that ST-T segment changes did not independently predict mortality, in contrast to the results from studies with a longer follow-up period.

Conclusions. This study shows that, in subjects with ST-T segment changes on their rest ECG, microalbuminuria may identify those at increased risk of all-cause and cardiovascular mortality. This suggests that ST-T segment changes reflect ischemic cardiac disease, particularly in the presence of other signs of generalized vascular damage. Therefore, measurement of urinary albumin excretion might improve cardiovascular risk profiling in the population at large, particularly in subjects with ECG signs of ischemic heart disease. However, the findings of this study need to be confirmed, and the added value of microalbuminuria to conventional cardiovascular risk factors needs to be further established before microalbuminuria can be incorporated into clinical practice.

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